Remarks/Arguments

Entry of the foregoing amendment is respectfully requested. In the specification, amendments to paragraphs [0052], [0058] and [0059] were made to delete unmatched parentheses; and in paragraph [0065], a hydrogen atom was added to complete proper bonding valency for the nitrogen atom of the sulfonamide. No new matter is added by the amendment to the specification or claims because the amendments are fully supported in the specification as filed.

Prior to entry of the present amendment, Claims 27-64 were pending in this application. With this amendment, Claim 30 has been canceled without prejudice, and Claim 27 has been amended to clarify what Applicants have always regarded as their invention; and no new claims having been added. Support for the amendment of Claim 27 is based on the incorporation of the subject matter from Claim 30. Claims 27-29 and 31-64 are pending after entry of the present amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Drawings:

The examiner noted that drawings were listed as filed with the application but no drawings are present in the file. Applicants informally referred to Figures 1-10 as "Drawings", and these Figures were filed with the application.

The 35 U.S.C. 112, first paragraph, Rejection:

Claims 27-64 were rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that "the claims give no indication as to what the compounds really are. One should be able, from reading of

the claims, determine what that claim does or does not encompass", the examiner further notes that there are "guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation", and concludes that "[t]he unknown compounds of the claims are not believed to meet the requirements of 35 U.S.C. 112, first paragraph." The Examiner cited *In re Wands* for factors to consider when assessing whether a disclosure would require undue experimentation.

Applicants respectfully disagree and traverse the rejection.

Enablement: The Legal Standard

When making a rejection on the ground of alleged lack of enablement, the Examiner has the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*; *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands*, 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance

provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762 63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled.

The Claimed Invention:

The present invention is from the field of designing new and improved methods for treating diabetes and/or its associated complications by modulating the activity of protein tyrosine phosphatase 1B ("PTP-1B"). In particular, the invention provides compounds that modulate the activity of PTP-1B by binding to a novel binding site ('the

PTP-1B exosite") that is distal to the active site of PTP-1B. Also provided are methods for treating immune system disorders by modulating the activity of T-cell protein tyrosine phosphatase ("TC-PTP"), and the inventive compounds modulate TC-PTP by binding to a novel binding site ("the TC-PTP exosite") that is distal to the active site of TC-PTP. In addition, the application discloses methods for identifying exosite inhibitors of PTP-1B and exosite inhibitor of TC-PTP. At the time the present invention was made, there was extensive information known in the art relating to PTP-1B and TC-PTP protein tyrosine phosphatases and their structures. See paragraphs [0020] to [0029]. Standard methods for the preparation and testing of biologically active compounds have been extensively reported in the literature, and are exemplified in the present application on pages 31-42, Examples 3-10. Accordingly, although unpredictability in the field of designing and preparing inhibitor compounds for PTP-1B and TC-PTP protein tyrosine phosphatases and designing methods for identifying inhibitor compounds for PTP-1B and TC-PTP protein tyrosine phosphatases may be viewed as relatively high, the unpredictability in the particular field to which the present invention as taught in the present application is of a lesser degree.

The level of ordinary skill in the art

It is well established that the level of skill in this technology is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

Guidance provided in the specification

Pages 4-7 describes PTP-1B and TC-PTP protein tyrosine phosphatases covering their structures and specifically the mechanism of action in the active sites. For example, the specific mechanism of hydrolysis is described in detail for the hydrolysis of a cysteinyl-phosphate intermediate compound. See paragraph [0024].

Paragraphs [0030] to [0035] exemplifies compounds that bind to the exosite of PTP-1B, showing specifically the adaptive binding site on PTP-1B listing the specific active residues. The formation of a specific adaptive binding site was further illustrated in detail with compound 5 (see page 8). In addition, Figure 2 illustrates a crystal complex of PTP-1B and compound 5, showing the presence of the crevice of the binding site, and the surface accessible surfaces of the particular binding residues. Furthermore, Figure 5 of the specification illustrates a few key interactions of the residues in the absence of an exosite ligand.

The particular compounds that may bind to the exosite, as exemplified by compound 5, causes specific changes in the binding site, including a displacement of the indole ring of Trp-291, a specific hydrogen bond of compound 5 with $N_{\delta 2}$ of Asn-193, and the disruption f the hydrogen bond between Asn-193 and Tyr-152 that mediates a conformational change in the phenolic ring of Tyr-152, which propagates a conformational change in the active site of PTP-1B that functionally inactivates the enzyme. The discloses further notes that in TC-PTP, may of the exosite-forming residues of PTP-1B are conserved including Asn-193, Lys-197 and Tyr-152.

Paragraphs [0036] to [0047] teach compounds that interact with specific exosite-forming residues of PTP-1B and TC-PTP. In particular, the interactions are described as those forming a hydrogen bon, a salt bridge, or a van der Waals contact with an exosite-forming residue.

The State of the Prior Art

As discussed on page 4 of the specification, PTP-1B and TC-PTP are protein tyrosine phosphatases, the signature motif of a PTP has been disclosed by Zhang as being found in a critical loop, and all PTP are characterized by their ability to hydrolyze p-nitrophenyl phosphate. In addition, there are known drug programs targeting PTP-1B and

TC-PTP that have focused on identifying active site inhibitors, and have succeeded in identifying potent active site inhibitors against target enzymes.

Proper conclusion based on the analysis of the in re Wand factors

The above analysis demonstrates that Applicants provided a significant amount of guidance to enable one skilled in the art to practice the invention. The Examiner alleges that "the claims give no indication as to what the compounds are ..." and that "one should be able, from reading of the claims, determine what that claim does or does no encompass."

As discussed, the legal standard merely requires that "there must be sufficient disclosure, either through illustrative examples *or terminology*, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *Enzo Biochem., Inc. v. Calgene, Inc., supra* - emphasis added. Furthermore, without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*; *In re Marzocchi, supra*. Indeed, it is legally improper to limit the assessment of enablement to the actual working examples.

Claim 27 of the present invention specifically recites a compound that inhibits PTP-1B and that interacts with at least one of the PTP-1B exosite-forming residues, and as amended herein, the specific group of PTP-1B exosite-forming residues are explicitly listed. The claimed compound of Claim 27 is described structurally with specificity as having a cyclic moiety, wherein a "cyclic moiety" is specifically defined in the specification as "a mono or polycyclic aliphatic or aromatic groups." See page 17, paragraph [0075]. Thus, as recited above, the compound of Claim 27 is clearly a compound with a cyclic moiety such as a mono or polycyclic aliphatic or aromatic group.

In addition, Claim 27 teaches that the compound is functionalized such that it is capable of forming a hydrogen bond, a salt bridge, or a van der Waals contact with at

least one of the exosite-forming residues. Therefore, Claim 27 (and claims that are dependent thereto) recites a compound having both specific structure and function.

It is clear from the disclosure that compounds of the present invention that have such specific structure and function, as illustrated with compound 5, are examples of compounds that inhibits PTP-1B (SEQ ID NO:1) and that interacts with at least one of the PTP-1B exosite-forming residues. See for example, the disclosure on pages 7-9, paragraphs [0030] to [0035].

As noted above, the disclosure teaches that the presence of a suitable ligand induces major conformational rearrangement in the enzyme, and one or more residues form an adaptive binding site. The conformational changes induced by the ligand is mediated by the interaction of at least three residues: Tyr-152, Asn-193, and Trp-291. In addition, as exemplified with compound 5, the benzofuran moiety of compound 5 displaces the indole ring of Trp-291, and the carbonyl oxygen of compound 5 makes a hydrogen bond with $N_{\delta 2}$ of Asn-193 so that the $N_{\delta 2}$ of Asn-193 is no longer available for hydrogen bonding to Pη of Tyr-152. Furthermore, Applicants teach that "a compound is said to interact with an exosite-forming residue ... if the compound forms a hydrogen bond, a salt bridge, or a van der Waals contact with an exosite-forming residue." See paragraphs [0038] to [0040].

Here, the claims are definite and enabling because Applicants have taught both structure and function, and Applicants have clearly disclosed the functional characteristics of the compounds coupled with a disclosed correlation between structure and function. And, in view of the art and the extensive and detailed teaching provided in the specification, Applicants respectfully submit that one of ordinary skill in the art would be able to practice the present invention as claimed. Although some experimentation might be necessary to identify, design and prepare compounds that will specifically interact with a PTP-1B and TC-PTP exosite-forming residues by forming a hydrogen

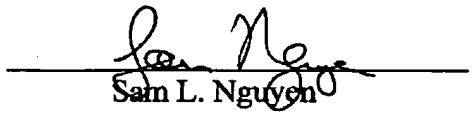
bond, a salt bridge or a van der Waals contact with one of the exosite forming-residues, which is within the scope of the pending claims, the fact that such experimentation might be needed is not sufficient to establish that the experimentation is undue.

Because the Examiner has not provided specific reasons why Applicants did not provide a sufficient disclosure to enable the claimed invention, a *prima facie* case of lack of enablement has not been established, and the burden remains on the Examiner. Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 27-29, and 31-64, as amended, under 35 U.S.C § 112, first paragraph.

Applicants respectfully submit that Claims 27-29 and 31-64, as amended, are in condition for allowance, and that allowance is respectfully solicited.

Respectfully submitted,

Date: March 8, 2005



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